REMARKS

Claims 42-66 and 69-126 are currently pending, with claims 42-45, 58-59 and 65 withdrawn from consideration. Claims 1-41 and 67-68 were previously cancelled.

After entry of this Amendment and Response, claims 46-57, 60-64, 66, 69-111 and 113-126 will be pending, as claims 42-45, 58-59, 65 and 112 have now been cancelled. Claims 46-57, 60-64, 66, 69-71, 73-79, 81-93, 95-105, 107-111, 113-120 and 122-126 have been amended.

Support for the amendments to the claims can be found in the specification, for example, at paragraphs 27, 28, 41 and 69-107; in the original claims; in Figures 8-10 and elsewhere in the specification.

Claim Objection

Claim 114 is objected to because, according to the examiner, "the hyphen between the words "target" and "wherein" in the first line should be replaced by a comma." Applicants have amended claim 114 by removing the hyphen and inserting a space. Accordingly, withdrawal of this objection is respectfully requested.

Claim Rejection under 35 U.S.C. § 112, Second Paragraph

Applicants acknowledge withdrawal of the previous rejection under 35 U.S.C. § 112, second paragraph.

Rejection under 35 U.S.C. § 103(a)

Claims 46-57, 60-64, 66 and 69-126 stand rejected under 35 U.S.C. § 103(a) as being obvious in view of Griffin *et al.* (U.S. Patent No. 5,756,291).

Applicants respectfully disagree.

Applicants' application is directed to aptamer regulators and methods for identifying aptamer regulators. As stated in paragraph [0041] on page 9 of the specification and illustrated

in Figures 8-10, aptamer regulators are aptamers wherein binding of the aptamer to a target regulates (activates or suppresses) binding of the target to a target partner, for example, by altering the conformation of the aptamer-bound target. As stated in paragraph [0072] on page 17 of the specification, a "target partner" is defined as a molecule that specifically interacts with a target. Without wishing to be bound by theory, paragraph [0071] of the specification and Figure 8 illustrate a possible mechanism of action for an aptamer regulator. Basically, binding of an aptamer to a target promotes a conformational change in the target that changes the nature of the target's interaction (*e.g.*, binding) with a target partner.

Indeed, independent claims 46, 47, 60, 66, 69 and 114 (and the claims that depend therefrom) are each directed to a method for identifying an aptamer that binds to a target wherein binding of the aptamer to the target increases the binding affinity of the target for a target partner relative to the affinity of the target for the target partner when the target is not bound by the aptamer.

The Examiner Has Not Established a *Prima Facie* Case of Obviousness

According to M.P.E.P. §§ 2142 and 2143, the examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. To reach a proper determination under 35 U.S.C. § 103, the examiner must step backward in time and into the shoes worn by the hypothetical person of ordinary skill in the art when the invention was unknown and just before it was made. The inquiry is whether the claimed invention as a whole would have been obvious at the time to a person having ordinary skill in the art. Knowledge of applicant's disclosure must be set aside in reaching this determination. In addition, impermissible hindsight must be avoided and the conclusion must be reached on the basis of the facts gleaned from the prior art. The key to supporting any rejection under 35 U.S.C. § 103 is the clear articulation of the reasons why the

claimed invention would have been obvious. Rejections on obviousness cannot be sustained with mere conclusory statements. There must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.

The examiner has not established a *prima facie* case of obviousness. The examiner discussed the scope and content of the cited reference and concluded that the cited reference did not disclose the claimed method steps. The examiner then further concluded that the claimed invention would have been obvious, that the skilled artisan would have been motivated to develop the claimed invention and that the skilled artisan would have a reasonable expectation of success. However, rejections based on obviousness cannot be sustained by mere conclusory statements. Rather, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.

The Claimed Invention Is Not Obvious

According to *KSR International Co. v. Teleflex Inc.*, 550 U.S. __, 82 U.S.P.Q.2d 1385 (2007) and M.P.E.P. § 2141, the framework for the objective analysis for determining obviousness under 35 U.S.C. § 103 is stated in *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). Obviousness is a question of law that is based upon underlying factual inquiries. The factual inquiries enunciated by the Court are as follows:

1) determining the scope and content of the prior art;

2) ascertaining the differences between the claimed invention and the prior art; and

3) resolving the level of ordinary skill in the pertinent art.

Objective evidence relevant to the issue of obviousness, if present, must also be evaluated. Such evidence, sometimes referred to as "secondary considerations", may include

evidence of commercial success, long-felt but unsolved needs, failure of others and unexpected results.

Even if a *prima facie* case of obviousness has been established, the claimed invention is not obvious in view of the cited reference.

Independent claims 46, 47, 60, 66, 69 and 114 (and the claims that depend therefrom) are each directed to a method for identifying an aptamer that binds to a target wherein binding of the aptamer to the target increases the binding affinity of the target for a target partner relative to the affinity of the target for the target partner when the target is not bound by the aptamer.

Scope and Content of the Cited Art

Griffin *et al.* ("Griffin") disclose methods for identifying oligomer sequences that specifically bind target molecules. The Griffin methods involve complexation of the target molecule with a mixture of oligonucleotides containing random sequences and sequences that serve as a primer for PCR under conditions wherein a complex is formed with the specifically binding sequences, but not with the other members of the oligonucleotide mixture. The complex is then separated from uncomplexed oligonucleotides and the complexed members of the oligonucleotide mixture are recovered from the separated complex using PCR. The recovered oligonucleotides may be sequenced. Successive rounds of selection using complexation, separation, amplification and recovery can be employed. The Griffin methods may also include negative selections steps.

The target molecules may be glycoproteins, proteins, carbohydrates, membrane structures, receptors and organelles, such as serum proteins, kinins, eicosanoids and extracellular proteins.

One embodiment of the Griffin method also uses multiple selections to select an oligonucleotide that binds to a complex between thrombin and thrombomodulin. Column 23, line 66 to column 24, line 13 recites:

> Several approaches may be used to select aptamers that block thrombin's activity towards fibrinogen and the thrombin receptor but do not affect the binding of thrombomodulin and activity towards Protein C. These approaches all involve the use of multiple selections to derive aptamers with highly specific properties. In the first example, a pool of oligonucleotides is subjected to two rounds of selection. The first round involves selecting oligonucleotides that bind to thrombin, the second round involves selecting those oligonucleotides that also bind to a complex between thrombin and thrombomodulin. Aptamers derived from such a dual selection strategy will be directed against regions of thrombin apart from the thrombomodulin binding site and will be unlikely to interfere with thrombomodulin binding and activity against Protein C.

Differences Between the Claimed Invention and the Cited Art

As stated above, independent claims 46, 47, 60, 66, 69 and 114 (and the claims that depend therefrom) are each directed to a method for identifying an aptamer that binds to a target wherein binding of the aptamer to the target increases the binding affinity of the target for a target partner relative to the affinity of the target for the target partner when the target is not bound by the aptamer. Therefore, aptamer binding to the target **facilitates** the binding of the target to the target partner. Aptamer regulators bind to a target and facilitate binding of the target to a target partner.

On the other hand, the Griffin reference discloses a method for selecting an aptamer that binds to a **pre-existing** protein complex between thrombin and thrombomodulin. Griffin does not disclose a method for selecting an aptamer that binds to thrombin and facilitates the binding of thrombin to thrombomodulin, which is how an aptamer regulator would function. As stated above, the purpose of the multiple selection method in Griffin is to select aptamers that block thrombin's activity towards fibrinogen and the thrombin receptor, but do not affect the binding

of thrombomodulin and activity towards Protein C. This is due to the fact that aptamers derived from such a dual selection strategy will be directed against regions of thrombin apart from the thrombomodulin binding site and will be unlikely to interfere with thrombomodulin binding and activity against Protein C. Therefore, Griffin does not teach a method for identifying an aptamer that binds to a target and facilitates the binding of the target to a target partner. In fact, the examiner has acknowledged this fact (see, for example, page 5 of the Office Action having a mailing date of 9/25/06, page 4 of the Office Action having a mailing date of 5/30/07 and page 6 of the Office Action having a mailing date of 2/5/08).

Contrary to the examiner's assertion, Griffin does not disclose eluting the bound aptamers with an agonist competitor, such as fibrinogen immobilized on a column, for further negative selection (page 6 of the Office Action having a mailing date of 2/5/08). Column 23, lines 49-51 recite "[a] negative selection could be performed in a similar manner with a fibrinogen substrate column". Not only does the cited sentence not disclose an elution step, but the entire paragraph in which the cited sentence resides does not disclose an elution step. And there is certainly no disclosure of an elution step using an agonist competitor.

In addition, applicants disagree with the examiner's assertion that it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the thrombin/thrombomodulin complex aptamer selection method by the negative-positive aptamer selection so that only the unbound oligonucleotides from the first round are used in the second round of selection and the thrombin/thrombomodulin complex-bound oligonucleotides are retained (page 6 of the Office Action).

Applicants disagree with the examiner's assertion above because it would render Griffin unsatisfactory for its intended purpose. The purpose of the multiple selection method in Griffin

is to select aptamers that block thrombin's activity towards fibrinogen and the thrombin receptor, but do not affect the binding of thrombomodulin and activity towards Protein C. If Griffin were to employ a negative selection process in this method, the negative selection would select against aptamers that bind thrombin or that bind thrombin outside of the thrombomodulin binding site. Both of these outcomes defeat the purpose of the Griffin method, which is to select aptamers that bind to a target (in this case, thrombin).

Secondly, even if the Griffin method is modified according to the examiner's suggestion, the modified method would, at best, only disclose a method for identifying an aptamer that binds to a **pre-existing** protein complex between thrombin and thrombomodulin. On the other hand, the claimed invention is directed to methods for identifying an aptamer that binds to a target wherein binding of the aptamer to the target increases the binding affinity of the target for a target partner and thus facilitates the formation of the target-target partner complex. Therefore, modifying the Griffin method according to the examiner's suggestion does not render the claimed methods obvious.

Applicants can't reconcile the examiner's assertion on page 6 of the Office Action that the skilled artisan would have been motivated to develop complex-favoring aptamers that function as an agonist that delivers the therapeutic ligand to the specific desired receptor and enhances the binding between the ligand and the receptor with the examiner's additional assertion on page 7 of the Office Action that "[e]ven though the Griffin patent does not express the agonist activity or the property of increasing binding affinity in the aptamers, this advantage would be recognized after the disclosed selection method during the evaluation of the final product". How could one find motivation after the fact?

In addition, applicants disagree with the examiner's assertion (page 6 of the Office Action) that there would have been a reasonable expectation of success given the general protocol of aptamer negative-positive selection protocol with suggested variations to obtained desired aptamers and the teaching that a wide variety of materials can serve as targets. Applicants note that there is a big difference between identifying an aptamer and identifying an agonist aptamer. Very few agonist aptamers exist. Even if one identifies an aptamer that binds to a target, very few aptamers have the additional property of agonist activity. Applicants note that the Griffin method is a single or two step process used to identify an aptamer that binds to a target, wherein, according to the examiner, agonist activity or the property of increasing binding affinity in the aptamers, may be determined after the disclosed selection during the evaluation of the final product. On the other hand, the method of the invention is a multi-step method that identifies aptamer regulators, *i.e.*, aptamers that bind to a target wherein binding of the aptamer to the target increases the binding affinity of the target for the target partner relative to the affinity of the target for the target partner when the target is not bound by the aptamer. Simply put, the Griffin method may identify an agonist aptamer or an aptamer regulator by chance, which property would be assessed after the selection method, whereas the method of the invention drives the selection process to identify an agonist aptamer or aptamer regulator from the outset.

Furthermore, applicants disagree with the examiner's assertion that Griffin discloses an aptamer selection method that can be modified according to any specific property that a skilled artisan desires (page 7 of the Office Action). From a policy standpoint, if the examiner's statement above is correct, then no future methods for identifying aptamers having any specific property will be patentable. For the reasons stated above, Griffin may not be modified to a

method for identifying an aptamer that binds to a target wherein binding of the aptamer to the target increases the binding affinity of the target for a target partner. As a result, applicants also disagree with the examiner's statement that applicants have only recognized another advantage that would flow naturally from following the suggestion of the prior art, which cannot be the basis for patentability when the differences would otherwise be obvious (page 7 of the Office Action).

Lastly, the examiner states that Griffin discloses the same or similar method steps with an obvious variation, and also discloses an allosteric change in the active site conformation of thrombin and an overlap of the thrombomodulin and fibrinogen binding sites on thrombin. This example appears in column 23, lines 14-51, which describe functional selection methods to isolate aptamers to thrombin that mimic the binding of thrombomodulin to convert the enzyme from a procoagulant protease to an anticoagulant protease by changing the substrate specificity of thrombin from fibrinogen to Protein C. Griffin further states that the thrombomodulin—dependent alteration in substrate specificity from fibrinogen to Protein C appears to be effected through a combination of an allosteric change in the active site conformation of thrombin and an overlap of the thrombomodulin and fibrinogen binding sites on thrombin. However, Griffin only teaches a method for selecting an aptamer that binds to thrombin using the basic SELEX method and then evaluating the aptamers for the additional property of agonist activity, such property being present purely as a matter of chance. Accordingly, Griffin does not teach or suggest the claimed method, which is a method for identifying an aptamer that binds to a target wherein binding of the aptamer to the target increases the binding affinity of the target for a target partner.

Griffin also does not disclose or suggest all of the method steps of the claimed invention. For example, independent claims 46, 47, 66 and 114 (and the claims that depend therefrom) each use a contacting step with conditions that disfavor efficient binding between the target and target partner, whereas the Griffin method does not. This step helps identify aptamer regulators, *i.e.*, aptamers that **facilitate** binding between the target and target partner. Including such a step in the Griffin method would render the Griffin method unsatisfactory for its intended purpose of identifying aptamers that specifically bind target molecules. Step e) and step d) of the methods of independent claims 60 and 69 (and the claims that depend therefrom), respectively, both require contacting nucleic acids bound to the target-target partner complex with an agonist competitor and amplifying the resulting eluted nucleic acids, thereby identifying aptamers that increase the affinity of the target for the target partner. This limitation is also not taught or suggested by Griffin, as Griffin does not disclose elution by competitive agonists.

Level of Ordinary Skill in the Pertinent Art

Applicants submit that a person having ordinary skill in the art would be a college educated scientist. Such a person would have the capability of understanding the scientific principles applicable to the pertinent art.

Accordingly, applicants submit that after analyzing the cited reference and the claimed invention in view of the *Graham* factors, the cited reference does not render obvious the claimed invention. Accordingly, withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

Applicants submit that the claims are not obvious in view of the cited reference. Accordingly, reconsideration of the rejection and allowance of the claims at an early date are earnestly solicited.

If there are any questions regarding this Amendment and Response or if the undersigned can be of assistance in advancing the application to allowance, please contact the undersigned at the number set forth below.

Respectfully submitted,

Michael G. Biro, Reg. No. 46,556
Sr. Patent Attorney
Archemix Corp.
300 Third Street
Cambridge, MA 02142
Direct: (617) 475-2324
Main: (617) 621-7700
Fax: (617) 621-9300